Eighth Annual Report 1999

Creutzfeldt-Jakob Disease Surveillance in the UK

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SECTION 1

Summary

The national surveillance programme for Creutzfeldt-Jakob disease (CJD) in the UK was initiated in May 1990. In 1999, the National CJD Surveillance Unit (NCJDSU) became a WHO Collaborative Centre for Reference and Research on the Surveillance and Epidemiology of Human Transmissible Spongiform Encephalopathies (TSEs). The information provided in this eighth report continues to provide evidence of a high level of case ascertainment. Detailed clinical and epidemiological information has been obtained for the great majority of patients. A high post mortem rate has been maintained through the period of the study 1990-1999. The success of the project continues to depend on the extraordinary level of co-operation from the neuroscience community and other medical and paramedical staff throughout the UK. We are particularly grateful to the relatives of patients for their help with this study.

The average number of cases of sporadic CJD identified annually since 1990 was higher than in previous surveillance periods extending back to 1970. It is impossible to say with certainty to what extent these changes reflect an improvement in case ascertainment and to what extent, if any, they reflect changes in incidence.

In 1990-1999 mortality rates from sporadic CJD in England, Scotland and Wales were, respectively, 0.74, 0.89 and 1.03/million/year. These rates are comparable to those observed in other countries in Europe and elsewhere in the world, including countries which are free of BSE. Mortality from sporadic CJD in Northern Ireland was lower (0.44/million/year). This difference is not statistically significant. There was some variation in the rates between the different regions within the UK but this variation is not statistically significant. The highest mortality from sporadic CJD was observed in the East Anglia region of England (SMR=129 [compared to the highest mortality rate of 126 in the South West in the last report]). Previous analyses have found no convincing evidence of space-time clustering, and this remains the case for the analyses in this report.

Up until 31 December 1999, there have been 51 deaths from variant CJD (vCJD) in the UK (and one further case was confirmed in January 2000). In 50 of these 52 cases the diagnosis has been confirmed neuropathologically. The clinical and neuropathological features of all these cases of vCJD are remarkably uniform and consistent with previous descriptions[1,2,3]. Statistical analysis has provided no evidence of space-time clustering of cases of vCJD nor that the rate of occurrence of new cases has increased with time since 1994.

Analysis of the incidence of vCJD by standard region suggests that the incidence of vCJD in the "North" of the UK may be higher than in the "South" (p=0.02). The possibility that this finding is due to more efficient case ascertainment in the "North" is not supported by analyses which reveal no difference in the incidence of sporadic CJD between "North" and "South". Further analyses are being undertaken to determine whether there may be differences in the regional exposure to putative risk factors for vCJD, including dietary exposures. However, the apparent differential incidence of vCJD between "North" and "South" should be treated with caution in view of the absence of an *a priori* hypothesis and the small numbers of cases on which this finding is based.

Risk factors for the development of vCJD include age, residence in the UK and methionine homozygosity at codon 129 of the prion protein gene - 49 cases of vCJD with available genetic analysis have all been methionine homozygotes. The analyses in this report do not provide evidence to suggest that there is an increased risk of vCJD associated with past surgery, previous blood transfusion, occupation or a range of dietary factors. However, the power of the case-control study, from which these results are derived, is limited by the small number of cases and controls. For some putative risk factors, such as blood transfusion or surgery, it will be many years before an accurate assessment of risk can be made because of the likely prolonged incubation periods.

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[1] Zeidler M, Johnstone EC, Bamber RWK, Dickens CM, Fisher CJ, Francis AF, Goldbeck R, Higgo R, Johnson-Sabine EC, Lodge GJ, McGarry P, Mitchell S, Tarlo L, Turner M, Ryley P, Will RG. New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 1997; 350: 908-910.

[2] Zeidler M, Stewart GE, Barraclough CR, Bateman DE, Bates D, Burn DJ, Colchester AC, Durward W, Fletcher NA, Hawkins SA, Mackenzie JM, Will RG. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet 1997; 350: 903-907.

[3] Ironside JW. New-variant Creutzfeldt-Jakob disease. Neuropathology 1998; 18(2): 131-138.

SECTION 2

2. Clinical Surveillance

The national surveillance of CJD was initiated in May 1990 in response to a recommendation in the Report of the Working Party on Bovine Spongiform Encephalopathy (Southwood Committee). The surveillance is funded by the Department of Health and by the Scottish Executive Health Department. The initial aim of the project was to identify any change in the pattern of CJD that might be attributable to the emergence of bovine spongiform encephalopathy (BSE). Such a change was recognised in 1996 when vCJD was first described. The project now aims to monitor the characteristics of all forms of CJD, to identify trends in incidence rates and to study risk factors for the development of disease. This report documents the findings from the NCJDSU (UK) in relation to cases of sporadic, familial, iatrogenic and vCJD diagnosed up to 31st December 1999 (with data ascertained up to 31st January 2000).

2.1 Sporadic Creutzfeldt-Jakob disease

Between 1st January 1970 and 31st December 1999, 837 cases of sporadic CJD were identified, of whom 5 cases were still alive on 31st December. Of these, 644 (77%) were classified as definite cases with the remainder classed as probable. Figure 1a shows the number of deaths each year from sporadic CJD for England and Wales between 1970 and 1999 and Figure 1b shows similar data for Scotland and Northern Ireland between 1985 and 1999. In England and Wales the number of deaths identified each year has increased from an average of about 10 per year at the beginning of the 1970s, to about 40 per year in the 1990s. A similar phenomenon has been observed in other European countries and this probably largely reflects improved case ascertainment. Over the shorter time period for which data are available for Scotland and Northern Ireland there is no clear secular trend, although the highest numbers of cases are seen in the two most recent years. Over the period 1990-1999 the average annual mortality rates from sporadic CJD per million population were 0.74 in England, 1.03 in Wales, 0.89 in Scotland and 0.44 in Northern Ireland, as shown in Table 1.

When account is taken of age and sex, the variation in recorded mortality between the different countries is not statistically significant ($p > 0.2$).

Figure 1a Deaths from sporadic CJD, England and Wales, 1970-1999

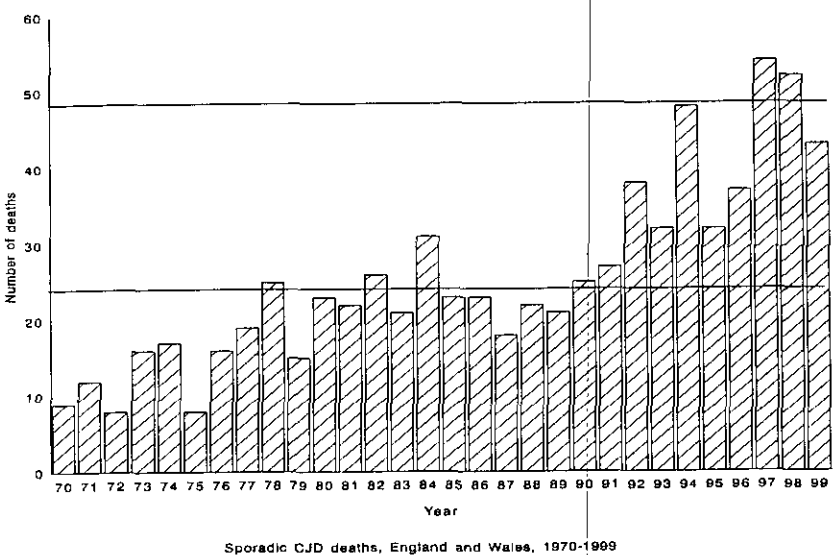
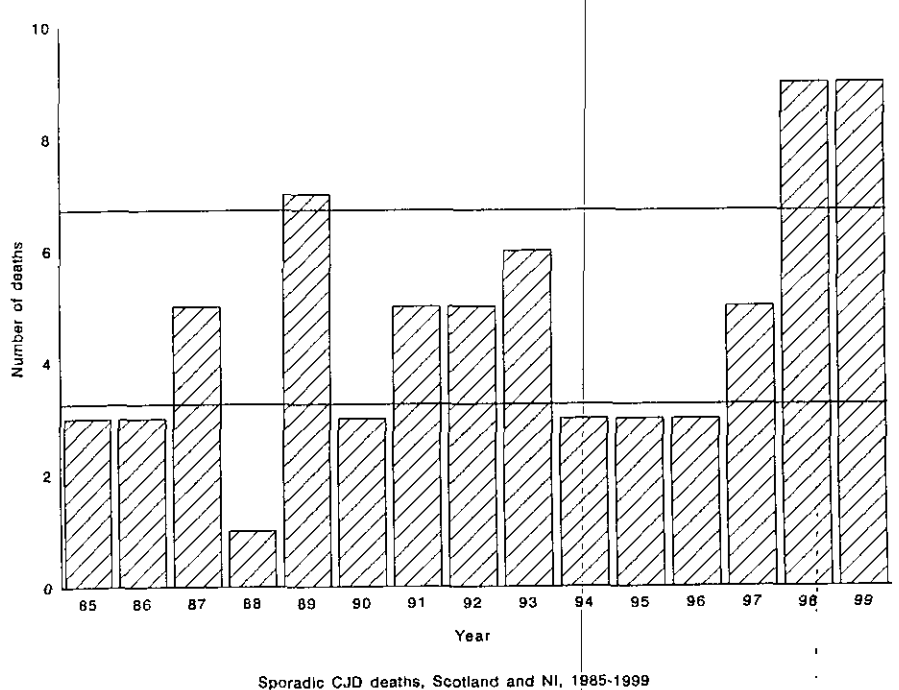


Figure 1b Deaths from sporadic CJD, Scotland and Northern Ireland, 1985-1999



Note: The horizontal lines indicate the number of deaths equivalent to crude mortality rates of 0.5 and 1 per million per year

Table 1 Deaths from definite and probable sporadic CJD by region and county of death: 01/05/1990 – 31/12/1999

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	1	
Cumbria	8	
Durham	4	25 (0.83)
Northumberland	2	
Tyne & Wear	10	
East Midlands		
Derbyshire	4	
Leicestershire	6	
Lincolnshire	4	22 (0.55)
Northamptonshire	1	
Nottinghamshire	7	
South East		
Bedfordshire	5	
Berkshire	7	
Buckinghamshire	2	
East Sussex	5	
Essex	13	
Greater London	46	118 (0.68)
Hampshire	8	
Hertfordshire	4	
Isle of Wight	1	
Kent	8	
Oxfordshire	6	
Surrey	5	
West Sussex	8	
North West		
Cheshire	6	
Greater Manchester	19	51 (0.82)
Lancashire	11	
Merseyside	15	
WALES		
Clwyd	3	
Dyfed	2	
Gwent	4	
Gwynedd	6	
Mid Glamorgan	6	
Powys	2	
South Glamorgan	2	
West Glamorgan	4	
TOTAL FOR WALES		**29 (1.03)**
NORTHERN IRELAND	7	**7 (0.44)**

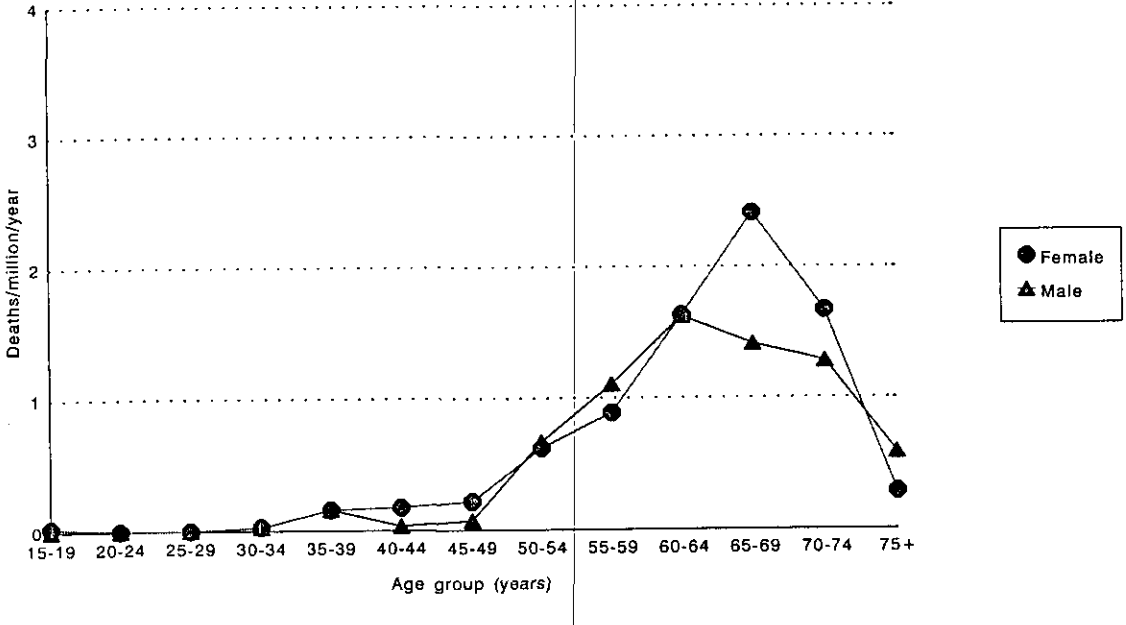
	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
Yorkshire & Humberside		
Humberside	3	
NorthYorkshire	8	
South Yorkshire	9	31 (0.64)
West Yorkshire	11	
East Anglia		
Cambridgeshire	3	
Norfolk	8	21 (1.03)
Suffolk	10	
South West		
Avon	8	
Cornwall	4	
Devon	10	
Dorset	10	48 (1.03)
Gloucestershire	5	
Somerset	4	
Wiltshire	7	
West Midlands		
Hereford & Worcs.	3	
Shropshire	3	
Staffordshire	6	32 (0.62)
Warwickshire	1	
West Mids (Met)	19	
TOTAL FOR ENGLAND		**348 (0.74)**
SCOTLAND		
Borders	1	
Central	3	
Dumfries & Galloway	0	
Fife	2	
Grampian	6	
Highland	1	
Lothian	12	
Strathclyde	16	
Tayside	1	
Islands (Shetland)	2	
Islands (Orkney)	0	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**44 (0.89)**

* Based on 1994 population by region (as published in ONS Regional Trends, 1996 edition) over the 9.67 year period of the study.

Figure 2a, 2b and 2c shows average annual age- and sex-specific mortality rates over the time periods 1970-89, 1990-94 and 1995-99, respectively. The median ages of cases at death during these time periods were 64, 66 and 65 years, respectively. In all three time periods, the mortality rates below 40 years of age were extremely low (< 0.16/million/year). Thereafter, in all three periods, the mortality rates increased to a peak in 65-74 year olds and then declined. The height of the peak appears to have increased over time (1.96 and 3.21 cases/million/year among 65-69 year olds during 1970-89 and 1990-94, respectively, and 3.27 cases/million/year among 70-74 year olds during 1995-99). The decline in the older age groups has become less dramatic over time with the rate in those over 75 years of age declining to 2.73 cases/million/year in 1995-99, which compares with 2.13 cases/million/year in 1990-94 and 0.38 cases/million/year in 1970-89. These observed differences in the rates in the older age groups over the three time periods could be explained by an increase in case ascertainment over time or a cohort effect.

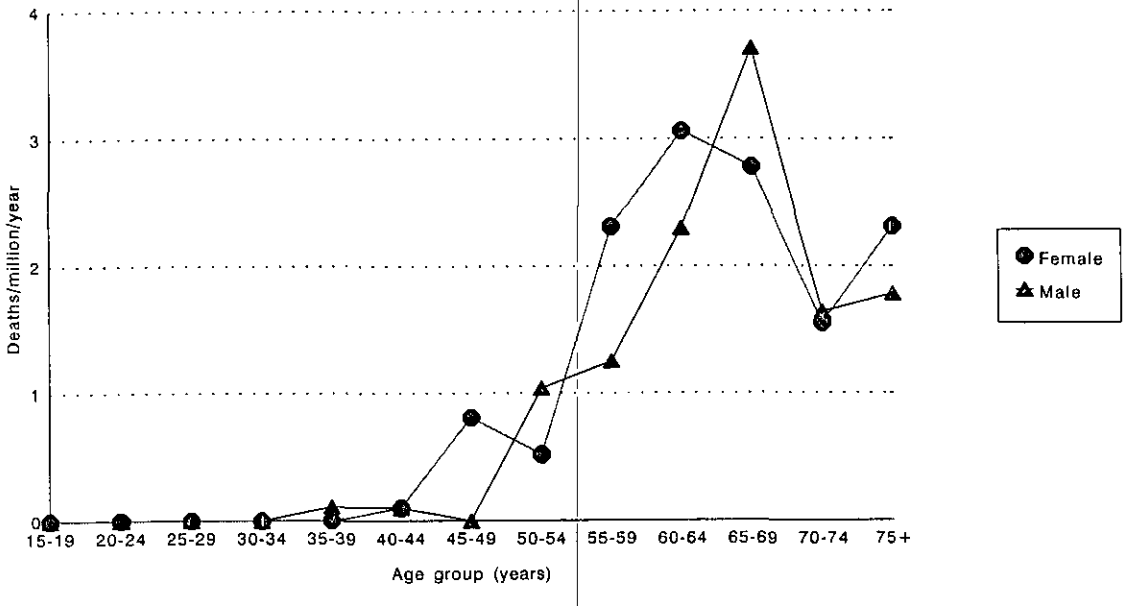
Figure 2a Age- and sex-specific mortality rates from sporadic CJD in the UK: 1970-1989

(NB: from 1970-1985 only England & Wales, thereafter UK)



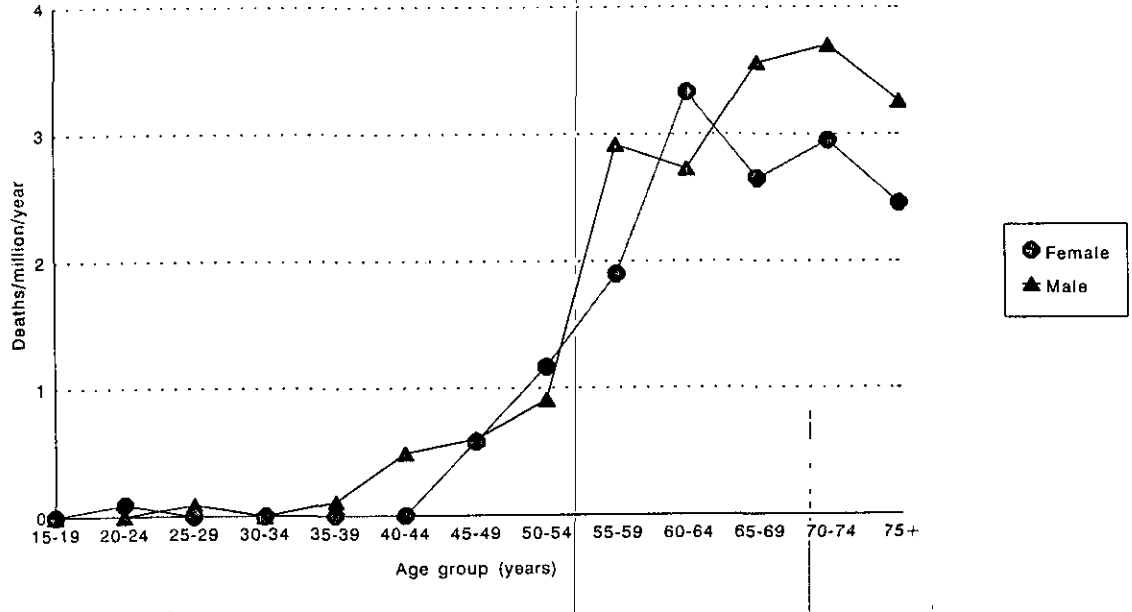
Mortality rates calculated using 1981 Census for GB and 1991 Census for NI

Figure 2b Age- and sex-specific mortality rates from sporadic CJD in the UK 1990-1994



Mortality rates calculated using *1991 Census*

Figure 2c Age- and sex-specific mortality rates from sporadic CJD in the UK 1995-1999



Mortality rates calculated using 1991 Census

An analysis of age specific trends from 1970 to 1999 (Figure 3) shows there has been an increase in mortality over time in all age groups, but that the greatest relative increase in mortality has occurred in those aged 70 years and above. Currently the mortality rate in this age group is similar to that in the age group 60-69 years. The temporal increases in mortality are statistically significant ($p < 0.001$ in the age groups 50-59, 60-69 and 70+ and $p=0.014$ in the younger age group, 40-49 years). These observations are consistent with improved case ascertainment in all ages, but with the greatest increase occurring in the elderly in recent years.

Figure 3 Trends in mortality from sporadic CJD by age: 1970- 1999

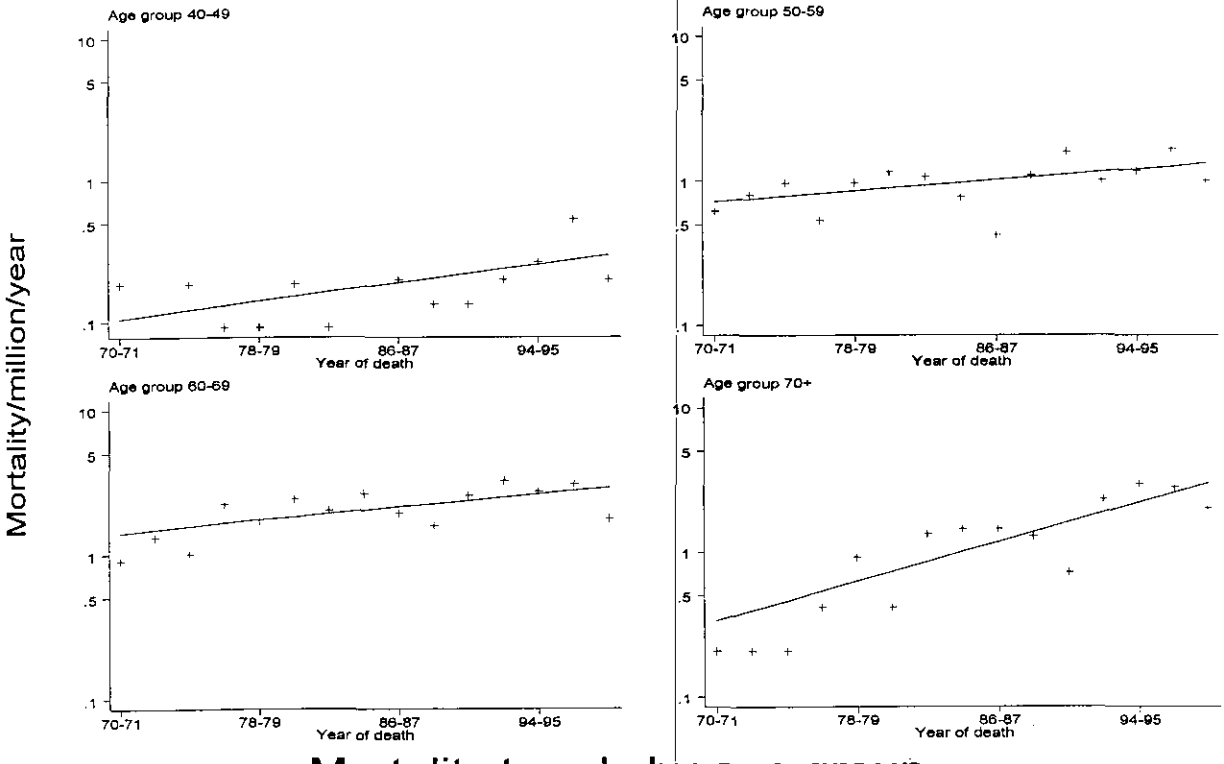


Table 2 presents, by 2-year period, the numbers of deaths underlying these trends. These data emphasise the very small numbers of cases of sporadic CJD occurring in individuals aged less than 50 years. They show clearly the substantial increase in the numbers of deaths identified among those aged 70 years and above, from around one per year in England and Wales in the early 1970s to around 20 per year in the UK in recent years.

Table 2 **Cases of sporadic CJD in England and Wales (from 1970) and the UK (from 1985) by two year period**

Age at death (years)	Year of death															Total[2]
	70-71	72-73	74-75	76-77	78-79	80-81	82-83	84-85[1]	86-87	88-89	90-91	92-93	94-95	96-97	98-99[2]	
10-19	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	**1(0)**
20-29	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	**2 (0)**
30-39	1	0	0	2	2	1	1	4	1	0	1	0	0	0	1(1)	**14 (1)**
40-49	2	0	2	1	1	2	1	0	3	2	2	3	4	8	7 (1)	**38 (1)**
50-59	7	9	11	6	11	13	12	9	5	13	18	12	14	20	24(2)	**184 (2)**
60-69	9	13	10	22	17	24	20	28	22	18	30	37	31	35	39(1)	**355(1)**
70 +	2	2	2	4	9	4	13	16	18	16	9	29	37	35	41	**237 (0)**
Total	**21**	**24**	**25**	**35**	**40**	**45**	**47**	**57**	**49**	**50**[3]	**60**	**81**	**86**	**99**	**113 (5)**	**832**[3] **(5)**

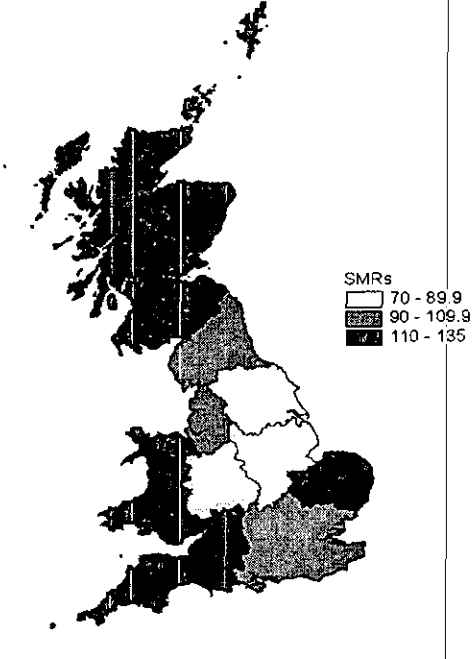
[1] Up to 1984, cases from England and Wales only. From 1985 onwards, cases from Scotland and Northern Ireland are included

[2] Deaths up to 31st December 1999. Numbers in parentheses indicate additional cases alive on 31st December 1999.

[3] Total includes one case whose age at death was unknown

Standardised mortality ratios (SMRs) for the 11 standard regions of the UK for the period 1st May 1990 to 31st December 1999 were calculated. Figure 4 shows the 10 regions of Great Britain. Northern Ireland has an SMR of 87. After adjusting for the age/sex distribution of the population, the variation in mortality rates between the different regions is not statistically significant ($p > 0.2$). Regions of relatively high mortality are East Anglia (SMR=129), the South West (SMR=126) and Wales (SMR=126). Low mortality rates were observed in East Midlands (SMR=72), the West Midlands (SMR=82) and Yorkshire & Humberside (SMR=83). The SMRs for the other five regions all lay between 87 and 117. The highest SMR (129 in East Anglia) arose from 21 cases observed compared with 16 expected, an excess of about 1 case every 2 years. In the South West and Wales the excess numbers of cases were approximately 10 and 6 respectively.

Figure 4 **Standardised mortality ratios (SMRS) by standard region, Great Britain, May 1990 - December 1999**



2.2 Genetics and sporadic CJD

The distribution of codon 129 genotypes in sporadic CJD has been analysed since the inception of the Unit in 1990. The overall distribution of codon 129 genotypes (73% MM, 12% MV, 15% VV) is consistent with findings from other European countries. There is no evidence of a significant change in the codon 129 distribution in sporadic CJD between the periods 1990-1995 and 1996-1999.

Table 3

Deaths from sporadic CJD	**MM (%)**	**MV (%)**	**VV (%)**
Deaths from 1 May 1990 - 31 December 1995	95 (75)	14 (11)	17 (13)
Deaths from 1 Jan 1996 - 31 December 1999	82 (70)	15 (13)	20 (17)
Total	177 (73)	29 (12)	37 (15)
Normal caucasian population pooling data from five studies[4]	(39)	(50)	(11)

2.3 Variant Creutzfeldt-Jakob disease

Up to 31st December 1999, 51 cases of vCJD had been identified in the UK (49 definite, 2 probable), and a further case was confirmed in January 2000. Twenty- eight (54%) of the 52 cases were women. The median age at onset of disease was 28 years and the median age at death 29 years (compared with 65 years for the median age at death for sporadic CJD). The two youngest cases were aged 14 years at onset while the oldest case was aged 53 years. All cases for whom genetic data are available (49) were methionine homozygotes at codon 129 of the PrP gene. The median duration of illness was 14 months (range 7-38). The median delay between onset of disease and confirmation of the diagnosis of vCJD was 15 months (with a range 7.2 - 32.0 months). This has not decreased over time.

[4] Alperovitch A, Zerr I, Pocchiari M, et al. Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease. Lancet 1999; 353: 1673-1674.

The number of deaths (11) in the last quarter of 1998 was higher than previous quarters. In 1999 the number of deaths reverted to about 3 per quarter, similar to numbers observed in quarters prior to the last quarter of 1998 (Figure 5). Analyses which adjust for delays in reporting and confirmation have found no evidence that the incidence rate of vCJD has increased significantly during the period 1994-1999 (N. Andrews, personal communication).

Figure 5 Cases of vCJD by date of onset

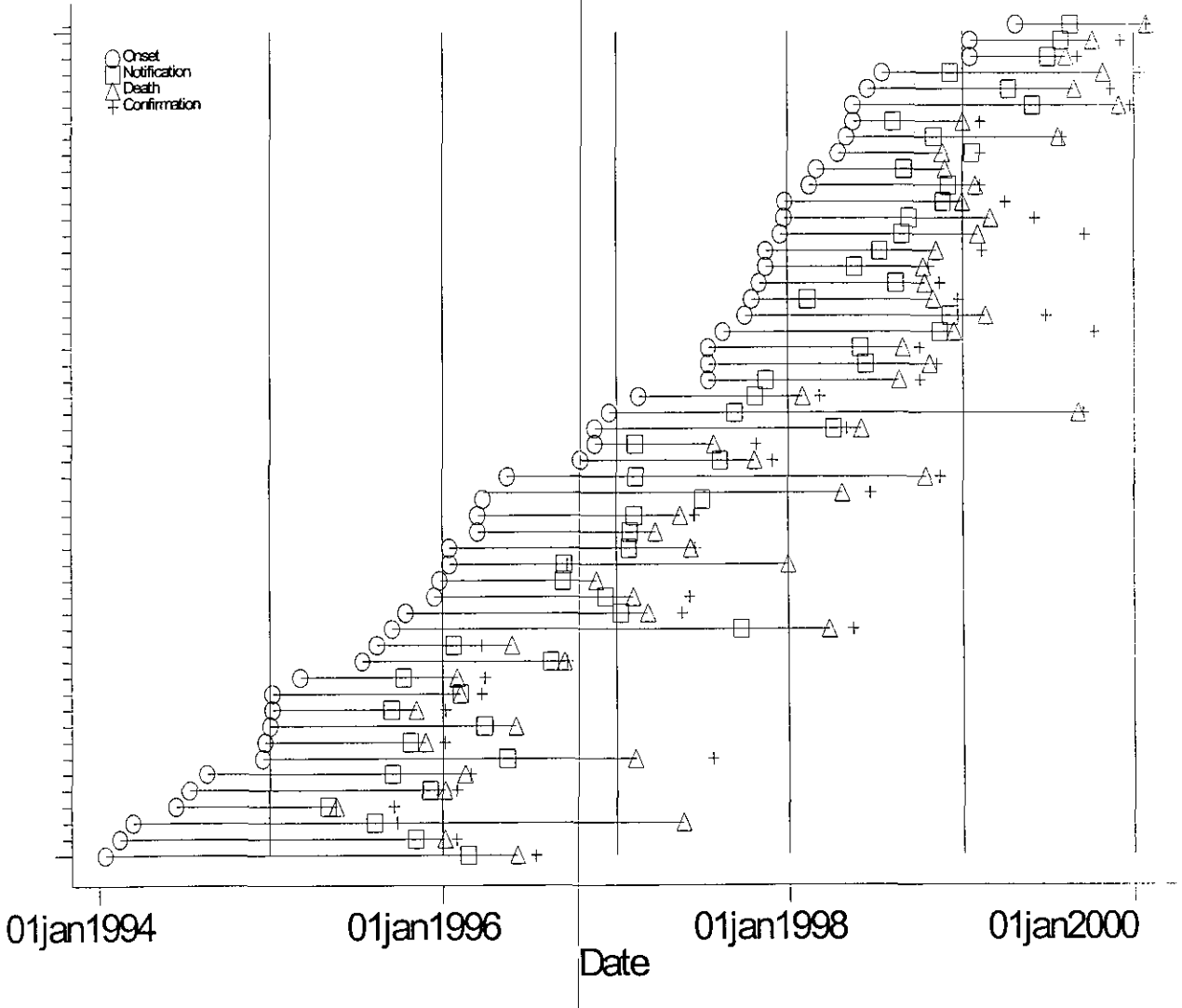


Figure 6 and Table 4 show the geographical distribution, by place of residence at onset, of the 52 cases of vCJD with onset in the UK. This shows that the cases to date have been widely spread geographically.

Figure 6

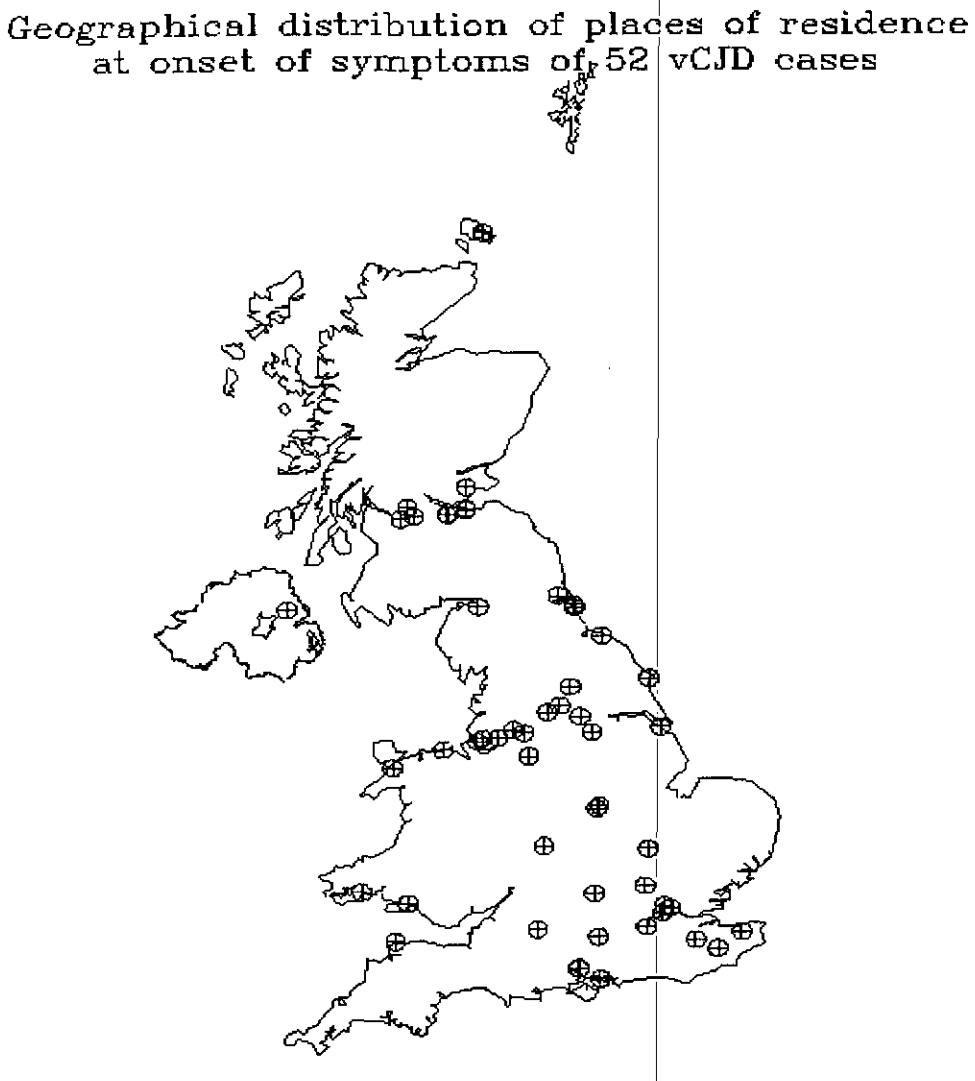


Table 4 Deaths from definite and probable vCJD by region and county of onset: 1 May 1995 - 31 January 2000

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
North		
Cleveland	1	
Cumbria	1	5 (0.34)
Durham	0	
Northumberland	0	
Tyne & Wear	3	
East Midlands		
Derbyshire	0	
Leicestershire	2	
Lincolnshire	0	2 (0.10)
Northamptonshire	0	
Nottinghamshire	0	
South East		
Bedfordshire	0	
Berkshire	0	
Buckinghamshire	0	
East Sussex	0	
Essex	0	
Greater London	4	
Hampshire	4	14 (0.16)
Hertfordshire	1	
Isle of Wight	0	
Kent	3	
Oxfordshire	1	
Surrey	1	
West Sussex	0	
North West		
Cheshire	2	
Greater Manchester	2	6 (0.20)
Lancashire	0	
Merseyside	2	
WALES		
Clwyd	1	
Dyfed	1	
Gwent	0	
Gwynedd	1	
Mid Glamorgan	0	
Powys	0	
South Glamorgan	0	
West Glamorgan	1	
TOTAL FOR WALES		**4 (0.29)**
NORTHERN IRELAND	1	**1 (0.13)**

	No of cases	Total no (mortality rate/million/ annum*)
ENGLAND		
Yorkshire & Humberside		
Humberside	2	
NorthYorkshire	1	
South Yorkshire	1	7 (0.29)
West Yorkshire	3	
East Anglia		
Cambridgeshire	1	
Norfolk	0	1 (0.10)
Suffolk	0	
South West		
Avon	0	
Cornwall	0	
Devon	1	2 (0.09)
Dorset	0	
Gloucestershire	0	
Somerset	0	
Wiltshire	1	
West Midlands		
Hereford & Worcs.	0	
Shropshire	0	
Staffordshire	0	1 (0.04)
Warwickshire	1	
West Mids (Met)	0	
TOTAL FOR ENGLAND		**38 (0.16)**
SCOTLAND		
Borders	0	
Central	0	
Dumfries & Galloway	0	
Fife	1	
Grampian	0	
Highland	0	
Lothian	4	
Strathclyde	3	
Tayside	0	
Islands (Shetland)	0	
Islands (Orkney)	1	
Islands (Western Isles)	0	
TOTAL FOR SCOTLAND		**9 (0.37)**

* Based on 1994 population by region (ONS Regional Trends, 1996 edition) over the 4.75 year period

The crude cumulative mortality rates for 1995-1999 based on 51 vCJD cases (excluding one case from Northern Ireland) and the population aged 16-54 years by region of residence in 1991 are shown in Table 5. The variation in mortality rates between the different regions is not statistically significant ($p>0.3$). Adjusting for age and sex distribution of the regions does not alter this finding ($p>0.3$). Regions of relatively high mortality are the Northern Region and Scotland, with cumulative rates of 3.14 and 2.98 per million of the population over the 5-year period. West Midlands and East Anglia have relatively low cumulative mortality rates of 0.36 and 0.93 per million of the population, respectively. Inspection of Table 5 reveals that the 4 most northern regions (Northern, North West, Yorkshire and Humberside and Scotland) contain the three highest rates and the fifth highest rate. The crude cumulative mortality rates for the "North" versus the "South" are shown in Table 6 and are statistically significantly different ($p = 0.02$). As before, this finding remains after adjusting for age and sex ($p=0.02$). However, these results must be interpreted with caution since this comparison was performed following examination of the data and was not based on a prior hypothesis. No such geographical association was found for sporadic CJD. Further analyses are being carried out and will be reported.

Table 5 Distribution of 51 vCJD cases by region of residence in 1991.

Standard region	**Population aged 16-54 at the 1991 census (%)**	**Number (rate/million[5]) of vCJD cases**
East Anglia	1,072,018 (4)	1 (0.93)
East Midlands	2,121,678 (7)	4 (1.89)
West Midlands	2,749,699 (9)	1 (0.36)
Northern	1,592,257 (5)	5 (3.14)
North-West	3,293,814 (11)	6 (1.82)
South-East	9,469,745 (32)	14 (1.48)
South-West	2,379,370 (8)	3 (1.26)
Yorkshire & Humberside	2,567,630 (9)	7 (2.73)
Scotland	2,684,004 (9)	8 (2.98)
Wales	1,461,006 (5)	2 (1.37)
Total	**29,393,174 (100)**	**51 (1.74)**

[5] over the five years 1995-1999

Table 6 Comparison of vCJD rates in 4 northernmost regions with those further south according to place of residence in 1991

Standard region	Population (millions) aged 16-54 at the 1991 census (%)	Number (rate/million) of vCJD cases
"North" (North West, Yorkshire & Humberside, Northern, Scotland)	10.1 (34)	26 (2.57)
"South" (South West, South East, Wales, West Midlands, East Midlands, East Anglia)	19.3 (66)	25 (1.30)
Total	**29.4 (100)**	**51 (1.73)**

2.4 An analysis of clustering of vCJD

An analysis to look for possible clustering of the places of residence in 1991 of 48 vCJD was performed (48 being the number of confirmed cases at the time of analysis). The year 1991 was chosen as it lies somewhere between when peak exposure to BSE agent is expected to have been if the SBO ban was effective in preventing human exposure to the BSE agent (1989) and when peak exposure is expected to have been if SBO ban was largely ineffective (1992/1993). Also, accurate small area census data by age are available for 1991.

The places of residence in 1991 of 48 vCJD cases were identified and the grid references for their census enumeration districts recorded. All possible pairs of cases were then examined to determine how close together the cases were living in 1991. The numbers of pairs of cases living within 1, 5, 10 or 20 km of each other were recorded.

To determine the expected distributions of the numbers of pairs of people in the UK population living within these distances of each other, enumeration district level data from the 1991 census was used. The age distribution of the 48 vCJD cases in 1991 was used to draw repeated age-weighted samples of 48 individuals from the census data. For each of

these repeated samples the numbers of pairs of individuals living within 1, 5, 10 or 20km of each other were computed. One thousand independent samples were drawn.

The results show that no pairs of cases were observed living at a distance of less than 1km (Table 7). There were 5 pairs of cases living within 5 km of each other, 9 within 10 km of each other and 24 within 20 km of each other. These observed numbers of pairs of cases do not represent an excess over the numbers that might be expected by chance, in the absence of any geographical clustering. This analysis provides no evidence for local clustering of vCJD cases.

Table 7 Numbers of pairs of cases living within 1 km, 5 km, 10 km and 20 km of each other in 1991.

	Number of pairs at a distance of			
	< 1 km	< 5 km	< 10 km	< 20 km
Pairs of cases (observed)	0	5	9	24
Median of 1000 random samples	0	4	9	27
95th percentile of 1000 random samples	1	7	18	48
99th percentile of 1000 random samples	2	10	22.5	63

2.5 Iatrogenic Creutzfeldt-Jakob disease

Since 1970, up to 31st December 1999, 40 cases of CJD attributable to iatrogenic exposure have been identified, 6 in individuals receiving dura mater implants and 34 in individuals who had received human-derived growth hormone (hGH) or gonadotrophin. The mean age at death of the latter group was 29½ years (with a range of 20-45 years) and for the dura mater cases was 43 years (range 27-59 years).

The first identified iatrogenic case was a dura mater recipient who died in 1979. The first hGH-related death occurred in 1985. Between 1st May 1990 and 31st December 1999 there were 29 CJD deaths in hGH recipients, an average of nearly 3 deaths per year.

2.6 Familial Creutzfeldt-Jakob disease

Thirty-five cases of familial CJD have been identified since 1970, excluding cases of GSS. Of these, 33 were resident in England and 2 were resident in Wales. Thirteen of the cases had insertions in the coding region of the PrP gene, 9 carried the mutation at codon 200 (Glu-Lys), 2 at codon 178 (Asp-Asn, both with methionine at codon 129), 1 at codon 117 (Ala-Val) and 1 at codon 210 (Val-Ile). Nine were identified as familial on the basis of relatives known to have had CJD (one with a relative known to have an insertion, one with a relative known to have the codon 200 mutation). The mean age at death was 55.6 years (with a range 38 - 68 years).

2.7 Transfusion Medicine Epidemiology Review

A collaborative study between the CJDSU and the UK Blood Transfusion Services has been in progress since 1997 to examine the possibility of transmission of CJD via blood transfusion. Patients with sporadic CJD and matched controls, who were reported to have donated blood, were identified and a single look-back exercise was performed. The details of the recipients who received components from these donors are held on the CJDSU database in order to check whether any subsequently develop CJD. This process was extended to vCJD cases. So far, 30 recipients have been identified in the CJD study and 12 in the vCJD study. None has appeared as suspect cases on the CJDSU register.

The reverse process is also underway. The study group is sporadic CJD patients and matched controls who have received blood. The relevant donors are traced and then linked to the CJDSU register. To date, 282 donors have been identified and none appear on the register. This study was also extended to vCJD. Only one vCJD patient was known to have received blood; 103 blood components were involved. None of the donors appear on the register.

(Collaborators on this project: Dr P.E. Hewitt and Dr C.A. Llewelyn).

2.8 Study of Progressive Intellectual & Neurological Deterioration (PIND)

The aim of this project is to use the mechanism of the British Paediatric Surveillance Unit to identify all cases of progressive intellectual and neurological deterioration in children in the UK, particularly those with features suggestive of vCJD. All cases are discussed by an expert neurological advisory group of seven paediatric neurologists which allocates the cases to a diagnostic category.

After 29 months of surveillance, 773 children have been reported. 570 cases have been discussed by the expert group. Of these, 322 have been classified as progressive intellectual and neurological deterioration with a recognised cause. 150 have yet to be allocated to a diagnostic group (pending further investigations and follow-up). 24 have been classified as idiopathic progressive intellectual and neurological deterioration (non-CJD). '220 have been classified as 'no case'. 56 cases are in the process of being followed up. So far one case of definite vCJD and 2 suspected cases have been identified.
(Collaborators: Dr C. Verity, Dr A. Nicoll, Ms G. Devereux).

2.9 Extent of misclassification of death from CJD Study

The NCJDSU collaborated with the Office of National Statistics and the London School of Hygiene and Tropical Medicine in this study. 1485 deaths from selected neurological disorders were identified in people aged 15-44 years in England during 1979-1996. All traceable clinical records (705,48%) were then reviewed to determine whether any cases of sporadic CJD or vCJD may have been misclassified as another illness. No new cases were detected in this sample of deaths which were considered most likely to have included any misclassified deaths. This provides some support for the completeness of CJD surveillance in England during this period.[6]
(Collaborators: Dr A. Majeed, Professor M. Coleman)

[6] Majeed A, Lehmannn P, Kirby L, Knight R, Coleman M. Extent of misclassification of death from Creutzfeldt-Jakob disease in England 1979-96: retrospective examination of clinical records. BMJ 2000; 320: 145-7.

SECTION 3

3. Case-Control Study

Methods

A case-control study of CJD has been carried out in the UK since May 1990 to investigate potential risk factors for the disease. Relatives of patients with suspect CJD have been interviewed using a standard questionnaire which includes a wide range of questions relating to putative risk factors for CJD including occupational, dietary and medical history. Up until 1997, for each suspect case, a patient at the same hospital was identified as a control. At the end of 1997 the design of the study was changed. Instead of hospital controls, it was decided to recruit community controls, matched for sex and age ± 4 years, through general medical practices (4 for each case of vCJD and one for each case of sporadic CJD). When possible, a relative of the same degree as for the case was interviewed using the standard questionnaire. If this was not possible the control was interviewed directly using the standard questionnaire. These community controls would be more suitable for the investigation of potential medical risk factors. Ethical clearance for the revised study design was received from the Multi-Centre Research Ethics Committee for Scotland in October 1998. In addition to the community controls, the revised protocol specifies that a further control group will consist of individuals referred to the CJDSU as suspect cases of CJD who are subsequently shown to have some condition other than CJD. This control group has been used in the analyses presented in this report.

Since the end of 1998, Local Research Ethics Committee (LREC) approval has been sought for each general practice in the study. Following each LREC approval, the complex and time consuming process of control recruitment commenced. By the end of 1999, 5 control risk factor questionnaires had been completed (relating to 2 vCJD cases).

Variant CJD

Because few community controls have been recruited to date, the analyses are based on data from 51 cases of vCJD and 27 controls - individuals who were referred to the CJDSU as

suspect vCJD and who either subsequently recovered (9), or who developed another pathological diagnosis (11) or who are thought very unlikely to be cases of vCJD (that is, recovery or an alternative diagnoses is expected) (7). These controls are not age- or sex–matched to the cases and their basic demographic characteristics are shown in Table 8. The median age of the controls is slightly older than the cases, 32 years compared with 28 years, but this does not reach statistical significance (p=0.092).

Table 8 Demographic characteristics of cases of vCJD (n= 51) compared to controls (n= 27)

	Gender		Median age at onset (years)	Range of age at onset (years)
	Males (%)	Females (%)		
Cases	24 (47)	27 (53)	28	14- 53
Controls	12 (44)	15 (56)	32	11- 58

3.1 Medical risk factors for vCJD

Thirty-one of the cases were reported to have had some sort of operation/surgical procedure (other than dental procedures) prior to the onset of their illness compared with 19 controls (Table 9). There is no evidence to suggest that cases were more likely than controls to have had operations in the past.

Table 9 Reported operations/surgical procedures from 51 cases of variant Creutzfeldt-Jakob disease and 27 controls.

	% of cases (n = 51)	% of controls (n= 27)
Any operation	61 n=31	70
Abdominal operation[1]	22	26
Neurological operation	0	0
Orthopaedic operation	10	7
Eye operation	2	7
Tonsillectomy	8	19
Appendicectomy	4	19

[1]Includes appendicectomy

Table 9 also shows that when specific operations/surgical procedures are examined, cases do not appear to have had more operations compared with controls.

Five of the 51 cases were reported by relatives to have had a history of blood transfusion compared with 2 of the 27 controls. It is of note in relation to the TMER study that a record of blood transfusion was not traced in 4 cases.

3.2 Dietary risk factors for vCJD

The reported consumption of various different meats and meat products by cases and controls in the period since 1980 (except for 5 cases and 4 controls where the period is from 1985 due to a change in the questionnaire) is shown in Table 10.

Table 10 Reported consumption of different types of meat from 51 cases[1] of variant Creutzfeldt-Jakob disease and 27 controls[2].

	% of cases (n=51)	% of controls (n=27)
Beef	98	96
Sausages	88	93
Burgers	88	88
Meat pies	86	87
Venison	25	22
Veal	18	35
Brain	0	4

[1] In 5 cases the dietary history was recorded from 1985 onwards. In the remainder it was taken from 1980.
[2] In 4 controls the dietary history was recorded from 1985 onwards. In the remainder it was taken from 1980.

Almost all cases and controls were reported to have eaten beef, sausages, burgers and meat pies. Thirteen cases and 6 controls were reported to have eaten venison ($p>0.7$), while 9 cases and 9 controls were reported to have eaten veal ($p=0.096$). Only one control was reported to have eaten brain. Looking at frequency of consumption of beef, cases were reported to have eaten beef more frequently than controls (Table 11), however this was not statistically significant ($p>0.2$). A similar analysis carried out for last year's report (1998) using hospital controls showed that cases were reported to have consumed beef more frequently than

controls (p=0.02). It was suggested that this finding may have been due to recall bias. This conclusion is supported by the analysis carried out in this year's report.

However, while these latter findings are consistent with there being no association, we cannot exclude the possibility that such associations exist.

Table 11 Frequency of consumption of beef by 51 cases of vCJD and 27 controls

Frequency of consumption	% of cases (n= 51)	% of controls (n= 27)
< 1/ month	16	22[1]
once a month or more	30	41
more than once per week	54	37

[1]includes one control who never ate beef

We also analysed the frequency of consumption of three food items, which may have contained mechanically recovered meat (MRM) (burgers, meat pies and sausages). When a person had different consumption rates of each of these food items reported, they were categorised according to the highest frequency of any of the food items. As can be seen in Table 12, there is widespread consumption of these food items in both cases and controls, with no significant difference between them (p>0.2).

Table 12 Frequency of consumption of burgers, meat pies and sausages by 51 cases of vCJD and 27 controls

Frequency of consumption	% of cases (n= 51)	% of controls (n= 27)
< 1/ month	10	19[1]
once a month or more	39	41
more than once per week	51	41

[1]includes one case and one control who never ate burgers, meat pies or sausages

Three cases (6%) and three (15%) controls reported that they had been vegetarians for a period of at least one year (p > 0.4).

3.3 Occupation and variant CJD

Table 13 presents a list of specific occupations for cases and controls, which were examined as potential at risk occupations for vCJD. Fourteen cases reported working in the catering industry compared with 5 controls, which was not statistically significant ($p>0.4$). Four cases worked in the meat industry and 3 in the medical/ medical related profession compared with 2 and 3 controls, respectively.

Table 13 Reported life- *time occupations* from 51 cases of variant Creutzfeldt-Jakob disease and 27 controls.

	% of cases (n=51)	% of controls (n=27)
Medical/ paramedical/ nursing/ dentistry	6	11
Animal laboratories	0	0
Pharmaceutical laboratories	0	0
Other research laboratories	0	4
Animal farming/ veterinary medicine	6	4
Meat industry (butcher's/ abattoirs/ rendering plants, etc.)	8	7
Catering industry	27	19
Other occupations involving animal products	2	0

3.4 Conclusion

We have found no evidence of any dietary, iatrogenic or occupational risk for vCJD.

SECTION 4

Neuropathology

4.1 Statement of Progress

The neuropathology laboratory in the CJD Surveillance Unit continues to maintain an increasing workload in terms of both diagnostic and research activities. In particular, the activities of the protein laboratory have greatly expanded, to allow a more precise characterisation of all CJD cases. The neuropathology laboratory maintains close liaison with other neuropathology laboratories across the UK, which has been reinforced by the activities of the National Retrospective Review of CJD and Related Disorders. This helps facilitate autopsy arrangements across the UK, the collection and transport of diagnostic materials and the brain and tissue banking activities. The high post-mortem referral rates for suspected CJD cases have been maintained in 1999. We are most grateful to all the neuropathologists, general pathologists and their technical, secretarial and autopsy room staff for their continuing support of the National CJD Surveillance Project.

4.2 Surveillance and Workload during 1999

A detailed breakdown of laboratory activities is summarised in Tables 14 and 15. These demonstrate that the case workload in relation to the previous reported period (20 months) has been increased, with core diagnostic activities related to the identification of CJD cases in the UK. A number of cases of prospective CJD have been referred from Europe and other countries in the world, including one case that was subsequently confirmed as vCJD. As before, the commonest alternative diagnosis to CJD was Alzheimer's disease and dementia with Lewy bodies, which are diagnosed according to standardised international criteria. In addition to these, smaller numbers of rarer conditions were identified (see Table 14). In addition to these tabulated cases, diagnostic material in the form of stained slides is submitted

to the Unit for review; these cases do not appear in this file since no additional technical work is required in the Surveillance Unit laboratory.

Table 14 Breakdown of Laboratory Activities: Period 1st January 1999 – 31st December 1999

	CURRENT YEAR	PREVIOUS YEAR *(20 months)*
REFERRED CASES (UK)		
No evidence of CJD*	28	46
Iatrogenic CJD (GHT)	5	7
Gerstmann-Straussler-Scheinker	0	3
Fatal Familial Insomnia	0	0
Sporadic CJD*	46	64
vCJD*	14	17
Other †	11	19
Alzheimer's disease	10	15
Dementia with Lewy Bodies	4	8
Research Project (ocular material)	3	0
REFERRED CASES (EU)	12	17
REFERRED CASES (ROW)	2	22
TOTAL NUMBER OF CASES	135	218

NOTES

* In some cases, more than one specimen has been referred to the Unit and these cases have therefore been allocated multiple laboratory numbers.

† Other:

Multiple Sclerosis	1	Hepatic Encephalopathy	1
Mitochondrial Encephalomyelopathy	1	Demyelination	1
Hypoxia	1	B-Cell Lymphoma	1
Metastatic carcinoma	1	Multifocal Ischaemic Damage	1
Viral Encephalitis	1	Oedema & Mild Gliosis	1
Multifocal Calcifying Leucoencephalopathy	1		

Abbreviations:

GHT: Growth Hormone Therapy
EU: European Union
ROW: Rest of world

Table 15 Monthly breakdown of the number of paraffin blocks cut and stained in the CJD laboratory for diagnostic and research purposes (including CNS and other human tissues and non-human research specimens)

January 1999 - December 1999

	Blocks	Slides
January 1999	539	2165
February 1999	611	2331
March 1999	117	544
April 1999	172	743
May 1999	38	153
June 1999	296	1059
July 1999	368	1308
August 1999	435	1452
September 1999	161	642
October 1999	122	509
November 1999	197	720
December 1999	161	505
TOTAL	**3217**	**12131**

Monthly Average Block Total: 268
Monthly Average Slide Total: 1011

4.3 Protein Laboratory

The protein laboratory in the NCJDSU was established in June 1998 with the recruitment of Dr Mark Head from Columbia University (NYC). Since no previous report has been made to the Department, this report covers the period from the establishment of the lab until the present time.

4.3.1 Aims

1. Introduction of Western blot analysis into the NCJDSU repertoire of differential diagnostic tests for CJD and its subtypes, with particular reference to vCJD.
2. Research into pathogenesis and phenotypic variation of CJD.
3. Participation in the development of novel diagnostic tests for vCJD.

4.3.2 Western Blot Analysis

Background and Nomenclature

The classification of proteinase K resistant prion protein (PrP^{res}) isotypes found in the brains of patients suffering from CJD has proved controversial with the debate centering on the possible number and molecular size of the non-glycosylated PrP^{res} protease resistant PrP protein. This is an important issue since PrP isotypes may equate to "strains" of the infectious agent accounting for phenotypic variation within and between forms of CJD. Our results dictate that we adopt the nomenclature of Type 1 (21kDa) and Type 2 (19kDa) PrP^{res} isotypes. Further classification is possible on the basis of the proportion of the three glycoforms (di-, mono-, and non-glycosylated PrP) present. The defining characteristic of PrP^{res} from cases of vCJD, namely the predominance of diglycosylated PrP^{res} is referred to by us as Type 2B. Our experience with PrP^{res} isotyping and the place that it occupies in the diagnosis of vCJD is described in a forthcoming publication.

CNS Tissues

Analysis of all suspected CJD cases referred to the unit (where frozen tissue is available) is now routinely carried out and the results available within the same time frame as those from histological tests. Post-mortem brain tissue, usually frontal cortex, has been analysed from 155 cases of suspected or confirmed CJD and neurological controls. This includes both a retrospective survey of cases held in the NCJDSU brain bank and cases analysed on receipt of frozen brain tissue by the NCJDSU following autopsy, as part of the ongoing surveillance program in the UK. The breakdown of cases is considered according to final diagnosis as follows (Table 16):

Table 16

Diagnosis	*Type*		*PrP^{res} +ve CNS*
CJD	Sporadic		100/100
	Variant		38/38
	Iatrogenic	Growth hormone	3/3
		Dura mater graft	2/2
	Familial	GSS	1/2
		FFI	0/1
Other	Alzheimer disease		0/4
	Lewy body dementia		0/2
	Other		0/3

PrP^{res} positivity on Western blot analysis accurately distinguishes between CJD whether sporadic, variant or iatrogenic (143/143) and neurological diseases with an alternative final diagnosis (0/9). PrP^{res} in familial forms of CJD was less consistently observed (1/3), however the aetiology of these forms of disease are demonstrable by *PRNP* sequencing.

Since sporadic CJD is the major differential diagnosis for vCJD and these two classes represent the majority of cases examined, they are considered further. The PrP^{res} isotype determined by Western blotting is shown in conjunction with the *PRNP* codon 129 status, which is known to modify disease susceptibility and phenotype. Of the 138 PrP positive sporadic CJD and vCJD cases, unequivocal isotype classification could be made in 134 cases. Of these the codon 129 status is known in 123 cases and their distribution is shown below (Table 17):

Table 17

Diagnosis	**129**	**Type 1**	**Type 2A**	**Type 2B**	**Total**
sporadic CJD	M/M	51	8	0	59
	M/V	4	10	0	14
	V/V	3	12	0	15
Total		58	30	0	88
vCJD	M/M	0	0	35*	35*
	M/V	0	0	0	0
	V/V	0	0	0	0
Total		0	0	35	35

* includes one case outwith the UK

These results show isotypic/genotypic diversity in sporadic CJD, however this variation appears non-random. For example 58% of all sporadic CJD cases are methionine homozygotes with type 1 PrP^{res} and only 3% are type 1 valine homozygotes. The contention that these isotype/genotype groups represent distinct clinico-pathological entities of sporadic CJD will be the subject of future studies. Part of this data has been included in an in depth histological study of sporadic CJD in valine homozygotes which has been submitted for publication.

In contrast to sporadic CJD, vCJD is stereotyped, with all cases thus far examined being methionine homozygotes and having a 2B PrP^{res} isotype. Densitometric analysis of glycoform ratios is ongoing. However analysis of eight MM2 cases of sporadic CJD with an equal number vCJD cases (also MM2) show the glycoform ratio groups to be non-overlapping, confirming the usefulness of the type 2B pattern in the diagnosis of vCJD. The failure to find this glycoform signature in CJD diagnosed as sporadic in young M/V or V/V individuals suggests that these cases do not represent vCJD in these genotypes. A glycoform ratio more closely resembling vCJD is however found in GSS.

The biochemical basis of the type 1 and type 2 isoforms has been addressed by contributing sporadic CJD and vCJD brain tissue isotyped in the protein lab to an N-terminal sequencing study conducted in another centre.

Five cases of CJD that contained detectable PrP^{res} were seen that could not be accommodated in the above classification system. Two MM sporadic CJD, one VV sporadic CJD and a case of GSS displayed a non-glycosylated PrP^{res} mobility reproducibly intermediate between Type 1 and Type 2. Our own studies show that a similar mobility type results from metal ion chelation prior to proteinase K treatment of Type 1 extracts. We are currently investigating the possibility that these intermediate types represent endogenously or artifactualy metal-depleted PrP.

The remaining unclassifiable case was a young VV individual with atypical clinical features, referred to the NCJDSU from outside the UK. Isotyping of a cortical biopsy showed Type 1 PrP^{res}, however after a protracted illness, analysis of autopsy cortical material showed Type 2 PrP^{res} and a glycosylation ratio markedly different from the biopsy material and more closely resembling that of GSS. This finding and recently published data showing isotype diversity

in a subset of sporadic CJD cases has prompted us to undertake a neuroanatomical survey of isotypes in sporadic CJD and vCJD. Preliminary results confirm isotype diversity within and between cases of sporadic CJD but indicate a homogeneous isotype in vCJD.

Peripheral Tissues

The possible presence of CJD infectivity in peripheral tissues of individuals with preclinical CJD presents a risk to public health. It is therefore important to determine the tissue distribution of PrP^{res} as a surrogate marker for infectivity in peripheral tissues. The challenge involved in such studies is that PrP^{res} levels are lower than in the CNS. The Protein Lab is currently involved in the parallel development of three approaches to address this question, namely Dissociation Enhanced Lanthanide Fluoro Immuno Assay (DELFIA), Capillary Electrophoresis and modifications of the standard Western blot procedure. Initial studies of peripheral tissues by Western blotting proved inconclusive however centrifugal concentration of PrP^{res} has allowed us to increase the sensitivity of our Western blotting procedure by up to a factor of 100. Using this technique we have analysed post-mortem tonsil with the following results:

Table 18

Diagnosis	**Number of Cases**	**PrP^{res} positive**
Lewy body dementia	1	0/1
sporadic CJD	4	0/4
iatrogenic CJD (growth hormone)	1	0/1
vCJD	4	4/4

These studies confirm the specificity of tonsilar PrP^{res} to vCJD and show tonsilar PrP^{res} to be more extensively glycosylated than PrP^{res} from the brain of the same individual. The negative result from the growth hormone therapy iatrogenic CJD tonsil is of interest since it demonstrates that peripheral infection with the CJD agent may be insufficient in itself to result in a PrP^{res} positive tonsil. We plan to extend this work to: i) further cases of CJD, ii) other forms of CJD, iii) other lymphoreticular organs, iv) the peripheral nervous system, and v) organs commonly used for transplantation.

4.3.3 Other activities

i. Collaboration with Dr Andrei Schmakov (University of Edinburgh) on the expression of PrP^C in the human enteric nervous system.

ii. Analysis of PrP^C expression in the context of neurological disorders other than CJD (in collaboration with Prof. Jeanne Bell and Dr Neil McLennan, University of Edinburgh).

iii. Pilot study to asses the feasibility of using Xenopus oocytes as a model system in which to study the conversion of PrP^C to PrP^{Sc} (in collaboration with Dr John Connolly, Strathclyde University).

4.4 Brain banking activities

The bank of fixed and frozen tissues in the surveillance unit was used extensively in 1999 for research purposes within the unit and with collaborators in the UK and overseas (see Table 19). No problems were encountered with Year 2000 compatibility in the Tissue Bank, and this facility is now being reorganised to allow the most efficient storage of frozen brain and organ samples, blood, DNA and CSF samples.

4.5 Health and Safety

The laboratory was inspected by a representative of the National Health and Safety Executive. No major problems were identified in the laboratory as a result of this inspection. The laboratory continues to receive numerous requests for advice and guidance on the safe handling of CJD tissues, autopsy procedures, burial and cremation. Careful attention to Health and Safety protocols within the unit has resulted in no accidents occurring this year in the laboratory and no problems with the handling and transport of materials to and from the laboratory.

Table 19 National and International Requests for Fixed and Frozen Material from the CJD Surveillance Unit's Brain and Tissue Bank

January 1999 - December 1999

Recipient	No. of Cases	Recipient	No. of Cases
Professor C Abee, Alabama, USA	3	Dr P Minor, Hertfordshire, UK	4
Dr J Anderson, Cambridge, UK	3	Dr M Mirakhur, Belfast, N. Ire.	5
Dr N Bogdanovic, Sweden	4	Dr D Moffat, Eastbourne, UK	1
Dr L Bridges,Leeds, UK	4	Dr Morgan, Scarborough, UK	1
Dr J Broome, Liverpool, UK	2	Dr T Moss,Bristol, UK	2
Dr P Brown, Maryland, USA	3	Dr I Nauroz, Kirkcaldy, UK	1
Dr M Bruce, Edinburgh, UK	7	Dr J Neal, Cardiff, UK	6
Dr M Carey, Birmingham, UK	12	Dr C O'Brien, Swansea, UK	1
Dr J Cesbron, Lille, France	1	Dr R Perry, Newcastle, UK	1
Professor J Collinge, London UK	3	Dr J Polo, Santander,Spain	2
Dr D Crooks, Hull, UK	3	Professor S Prusiner, San Francisco, USA	12
Dr S Dealler, Leeds, UK	2	Dr Raafat, Birmingham, UK	1
Dr D Ellison, Southampton, UK	3	Dr H Reid, Manchester,UK	5
Dr M Esiri, Oxford, UK	1	Dr T Revesz, London, UK	4
Dr M Farrell, Dublin, Ireland	1	Dr K Robson, Nottingham,UK	1
Dr J Fraser, Edinburgh, UK	12	Dr E Ruban ,Leicester, UK	1
Dr P Gambetti, Ohio, USA	3	Professor A Sau, Marmara, Turkey	2
Dr J Geddes,London,UK	6	Dr Scoones, Middlesbourgh, UK	2
Professor F Gray, Cedex, France	1	Dr S Shanker, Bangalore ,India	1
Dr J Hope, Compton,UK	15	Dr R Somerville , Edinburgh, UK	2
Dr P Ince, Newcastle, UK	2	Dr M Stewart, Lancaster, UK	1
Dr G Jansen, Utrecht, Holland	5	Dr A Taratuto, Buenos Aires, Argentina	2
Dr C Jarius, Vienna, Austria	1	Dr W Timperley,Sheffield, UK	4
Dr R Kisilevsky, Ontario, Canada	1	Professor R Weller, Southampton, UK	3
Dr Kitamoto, Sendai, Japan	3	Dr S Wells, Bolton, UK	1
Dr S Lehmann, Montpellier, France	3	Dr S Wharton, Edinburgh, UK	1
Dr P Liberski, Lodz, Poland	2	Ms. L Wheatley, Leicester, UK	1
Professor J Lowe, Nottingham, UK	8	Dr H Whitwell, New Zealand	1
Dr J Mac Kenzie, Aberdeen, UK	2	Dr P Wilkins, London, UK	1
Dr D Mann, Manchester, UK	2	Dr Wright, Dunedin, New Zealand	1
Dr J Manson, Edinburgh, UK	1	Dr J Wyatt, Leeds, UK	6
Dr A Marshall, Essex, UK	2	Dr K Zarkovic, Zagreb, Croatia	5

4.6 Research Projects

The laboratory is involved in several major research projects in relation to vCJD, including a Retrospective Study of PrP in Tonsil and Appendix Tissues, and the National Retrospective Review of CJD and Related Disorders. The laboratory also contributes to the EC BIOMED2

neuropathology project headed by Professor Budka in Vienna and the BIOMED2 project for the Surveillance of CJD in the European Community (led by Professor Will). Quantitive studies in the neuropathology laboratory are incorporated into an EU-funded study (QAMRIC) which involves correlation and quantitation of all aspects of neuropathology and neuro-imaging in CJD. The unit is also involved in two parallel collaborative projects to develop biochemical techniques capable of detecting the abnormal isoform of PrP in human peripheral tissues, including blood. The first technique is Dissociation Enhanced Lanthanide Fluoro Immuno Assay (DELFIA) in collaboration with, Dr James Hope (IAH, Compton) and Dr Marc Turner (SNBTS, Edinburgh). The second is to employ Capillary Electrophoresis with Laser-Induced Fluorescence (CE-LIF) in collaboration with Dr Mary Jo Schmerr (National Animal Disease Center, Ames, IA, USA).

SECTION 5

Publications

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Ms D Best, Ms D Auras	Research Technicians
Dr M Head	Research Scientist (molecular and cell biology)
Ms BA Mackenzie	Neuropathology Database Manager/Secretariat
Ms A Honeyman, Mrs S MacDonald	Secretariat
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